ORIGINAL RESEARCH

A systematic characterization of the factors influencing polymerization and dynamic behavior of n-butyl cyanoacrylate

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ABSTRACT

Introduction Brain arteriovenous malformations are abnormal connections between arteries and veins without an intervening capillary bed. Endovascular glue embolization with N-butyl cyanoacrylate (NBCA) is an accepted form of treatment. The reported complication rates vary widely from 2% to 15%, and timing of polymerization appears to play a major role. Additionally, the interaction between NBCA and vessel surface as well as the presence of biological catalysts are poorly understood.

Methods Polymerization time was measured for mixtures of Lipiodol/NBCA of 50/50, 70/30, and 60/40. The influence of pH, temperature, and the presence of biological catalysts on polymerization time was investigated. Contact angles were measured on polyvinyl alcohol cryogel (PVA-C), silicone, and endothelial surfaces in a submerged aqueous environment to assess physical surface interactions. High speed video analysis of glue injection through a microcatheter was performed to characterize simulated coaxial flow.

Results NBCA polymerization rate increased with pH and temperature. A hydrophilic surface such as PVA-C was better than silicone at mimicking the physical properties of endothelium. Live endothelium provided a catalytic surface that at least doubled the rate of polymerization. Blood products further increased the polymerization rate in the following order (slowest to fastest): plasma, platelets, red blood cells (RBCs), and lysed RBCs. These factors could explain the discrepancy between in vitro and in vivo results reported in the current literature. High speed video analysis of NBCA injection showed dripping to jetting transition with significant wall effect which deviated from previous ideal assumptions.

Conclusions The determinants of NBCA polymerization rate are multifactorial and dependent mainly on the presence of biological catalysts coupled with flow related wall interaction.

BACKGROUND AND OBJECTIVE

Brain arteriovenous malformations (AVMs) are abnormal connections between arteries and veins without an intervening capillary bed.[1 2] Their prevalence ranges from 1 to 20 per 100 000 patients and, of these, approximately half will present with an intracerebral hemorrhage resulting in significant morbidity (30–40% per event) and mortality (10% per event).[1–6] Endovascular glue embolization with injection of N-butyl cyanoacrylate (NBCA) is an accepted form of treatment.[7–10] It is most often used as an adjunct to surgery or radiosurgery, although it can be sufficient as a standalone treatment in approximately 5–10% of cases.[8] In carefully selected cases, the cure rate with endovascular embolization can be higher, ranging from 20% to 50%.[7 11–15]

Although ethylene vinyl alcohol copolymer (sold by Covidien as Onyx) has quickly become a preferred liquid embolic agent at many centers, there are certain high flow AVMs (usually with fistulous components) where Onyx cannot be used. NBCA remains a mainstay of treatment in such situations but is also associated with complications. Most of the complications that occur during embolization with NBCA are related to polymerization rate.[7 8] A rate that is too fast may cause premature proximal feeding artery occlusion. Glue could then reflux and cause strokes. Conversely, a rate that is too slow could cause the glue to occlude the draining vein, or embolize to dural sinuses and even to the lung.[16–18] Premature venous drainage occlusion may raise the AVM intranidal pressure and trigger an intracranial hemorrhage.[19–21]

Existing scientific literature reports a wide range of polymerization rates with significant discrepancies between in vivo and in vitro results.[8 22 23] Furthermore, the interaction between glue and vessel surface, as well as the presence of biologic catalysts, are poorly understood. Therefore, despite its clinical use for over four decades (FDA approved in 2000 with use dating almost three decades prior),[9 10] there is still incomplete understanding of NBCA polymerization and injection behavior.[8] This has resulted in wide variation with respect to the degree of dilution (typically modified by altering glue/Lipiodol or glue/acetic acid ratio)[24] and injection technique (sandwich, wedge, or full column technique) used for NBCA embolization procedures.[7 8]

The decreasing amount of NBCA operator experience with the introduction of Onyx coupled with the incomplete understanding of NBCA behavior further exacerbates treatment risk for patients, especially in situations where NBCA is the only option. In this study, our aim was to systematically characterize the factors that influence NBCA polymerization in both static and dynamic environments. Such information could add to interventionalists' background knowledge and help supplement trainees' learning experience.

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METHODS

From previous studies[8 22–25] and our preliminary data, NBCA appears to behave differently in the presence of biological tissue compared with tissue free vessel substitutes. Static NBCA interactions were deconstructed into three categories: (1) influence of physical parameters (temperature and pH); (2) surface interaction between NBCA and vessel wall (both non-biological and biological); and (3) exposure to biological tissue. Histoacryl (Braun, Germany) was used in this study, which has the same composition as TruFill (Codman, USA).

The influence of pH and temperature on NBCA polymerization time was measured. The submerged droplet test method was employed where small droplets of NBCA (~0.1 mL) were deposited on an inert polyvinyl alcohol cryogel (PVA-C) surface using a syringe with a 25 gauge needle submerged in an aqueous environment. Clinically relevant mixtures of Lipiodol/NBCA of 50/50, 60/40, and 70/30 ratios were investigated. Polymerization times (at 37.4°C) were recorded for solution pH values of 4, 5.5, 6.5, and 7.4, corresponding to physiologic solutions of D5W, normal saline, Ringer's lactate, and Plasma-Lyte, respectively. These solutions provided an aqueous acellular and plasma free environment. Polymerization times (at pH=7.4) were also recorded for solution temperatures of 15, 20, 25, 30, 35 and 37.5°C.

The surface interaction between NBCA and the vessel wall was analyzed using the contact angle method with the important modification of performing all measurements in a submerged aqueous environment (Plasma-Lyte at 37.5°C). Native avian endothelium was used as the reference surface. Silicone (both plain and heparin coated) and PVA-C surfaces were tested as vessel substitutes and compared with the endothelial surface. Silicone was chosen due to its ubiquity and its status as a 'de facto' vessel substitute in numerous prior studies involving NBCA. PVA-C was chosen as a hydrophilic material that better replicates the physical properties of an endothelial surface.

To assess biological catalysts, the endovascular environment was separated into endothelial surface and blood products. The effect of endothelial surface was assessed by placing NBCA droplets on a flattened viable endothelial surface. The effect of blood products was further broken down into plasma, platelets, packed red blood cells (RBCs), and lysed RBCs. Polymerization times were measured by first placing a layer of each of the respective blood products on a PVA-C surface, followed by placing NBCA droplets onto the surface. All tests were performed at pH=7.4 and 37.5°C. As polymerization is a continuous process, polymerization times were measured for each glue concentration at three different time points: t_0, t_{50}, and t_c. t_0 is the time from initial glue deposition to the onset of polymerization, first observed when the surface of the glue droplet opacifies. t_{50} is the time to achieve a 50% change in height of the glue droplet (or 50% reduction in diameter in any direction). t_c is the time to near complete polymerization (over 95% polymerization based on continuous video observation). To further confirm t_c, we performed indentation tests on select glue droplets using an ASTM type OO indenter with a modified 10 g load.

To examine the dynamic behavior of the NBCA/Lipiodol mixture during microcatheter injection, high speed video analysis of glue injection was performed to characterize flow and simulate in vivo conditions. A flow circuit was constructed using a pulsatile pump with tubing connected to straight vessel substitutes made of heparin coated silicone (Medtronic, USA). A flow bypass circuit was connected parallel to the vessel substitute. A rotating hemostatic valve was connected upstream of the vessel substitute to allow microcatheter insertion (SL-10, Stryker). The dynamic behavior of NBCA/Lipiodol flow within the vessel was considered akin to coaxial flow, as described by Utada *et al*.[26]

At least three droplets were used for each glue formulation/test condition combination. Statistical significance was determined using a two tailed Student's t test, ANOVA, or χ^2 analysis, wherever appropriate. Results are expressed as mean±SD. Results were considered significant when $p<0.05$.

RESULTS

pH and temperature

The polymerization times for three different formulations of Lipiodol/NBCA were plotted against pH and temperature in figure 1A and figure 1B, respectively. Polymerization time decreased (indicating increasing polymerization rate) with increasing pH as well as increasing NBCA glue concentration. pH and glue formulation independently influenced polymerization time ($p<0.05$, two factor ANOVA). In figure 1B, as expected from reaction kinetics, increasing temperature caused a corresponding increase in polymerization rate. Although the brain is at body temperature during interventional procedures, the catheters are constantly flushed with ambient temperature solution. As such, the AVM nidus temperature could actually be slightly below body temperature. Temperature and glue formulation also independently influenced polymerization time ($p<0.05$, two factor ANOVA).

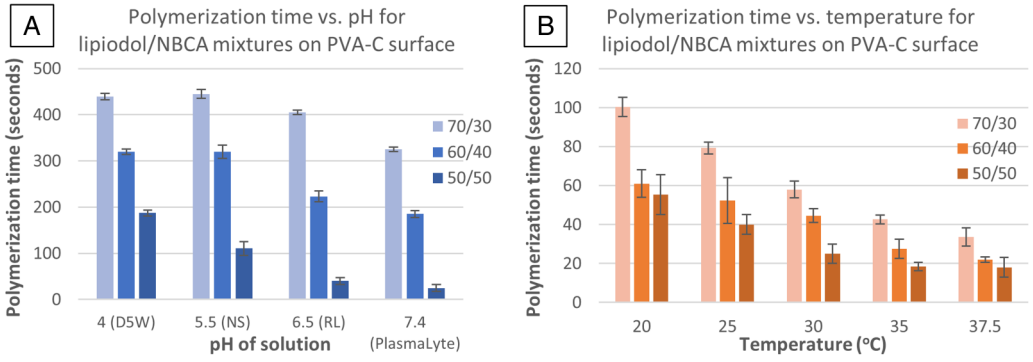

Figure 1 Polymerization time versus pH (A) and temperature (B) plots for three different clinically relevant mixtures of Lipiodol/n-butyl cyanoacrylate (NBCA) (70/30, 60/40, and 50/50). Polymerization time decreased with increasing glue concentration, solution pH, and temperature, indicating increasing polymerization rate ($p<0.05$, two factor ANOVA). PVA-C, polyvinyl alcohol cryogel.

Surface interactions

The submerged contact angle (figure 2A–D) of glue droplets on silicone (52±3°), heparin coated silicone (84±3°), and PVA-C (150±8°) were significantly different from each other. The contact angle on endothelium was found to be 151±3°. There was no statistically significant difference in contact angle between endothelial and PVA-C surfaces.

Biological catalysts

From previous studies[8 22–25] and our own observations, glue polymerization rate appeared to increase in the presence of biological tissue. Figure 2E, F show time lapse photographs of glue droplets (50/50) on an endothelial surface (pH=7.4, 37.5°C). Figure 2G, H shows glue droplets (60/40) on a PVA-C surface at 5 min with confirmatory indentation test. Glue droplets on both surfaces looked identical at t=0. However, as time progressed, glue droplets on the endothelial surface started to polymerize from the bottom up and flatten out. Complete polymerization occurred at approximately t=90 s. In contrast with this, glue droplets on the PVA-C surface opacified and mildly flattened initially but then changed very little as time went on. The indentation test in figure 2H shows a blue liquid streak running between the polymerized shell and the type OO indentor tip, confirming that the centers of glue droplets remained liquid.

Decomposition of the endovascular environment yielded the following major biological components: endothelium, plasma, platelet, and RBC. Their effect on glue polymerization time was further explored. Given that polymerization is a continuous process, the times t_o, t_{50}, and t_c were measured for each glue formulation and biological substrate combination, as shown in figure 3A–C. Table 1 shows the polymerization times on an endothelial surface. Overall, polymerization times decreased as the biological substrate varied from endothelium, plasma, platelets, packed RBCs, and lysed RBCs. Lysed RBCs appeared to result in the greatest decrease in polymerization time (corresponding to the greatest increase in polymerization rate).

Figure 3D shows an example of polymerization time measurements for the 70/30 mix on exposure to plasma. The glue appeared transparent on initial deposition at t=0 s. At t_0=2.4 s, the glue droplet opacified and began to deform. At t_{50}=7.5 s, the glue droplet flattened to approximate 50% of the original height and appeared more irregular. Finally, at t_c=116 s, polymerization was complete and the glue droplet lost its bluish hue while taking on an irregular multi-lobulated morphology.

In vivo simulation

Figure 4A–C illustrates the idealized model of coaxial flow, as previously described by Utada *et al*. The outside shell flow was akin to the blood flow in an AVM feeding artery while the central coaxial flow mimicked the microcatheter glue injection. As the injection rate increased, there appeared to be a transition from dripping to jetting flow.[26] Figure 4A–C shows the experimental observations (recorded at 240 fps, see online supplementary video included), where three distinct phases are noted. Phase 1 (figure 4A) consisted of dribble flow that lasted only 1–2 s before the whole microcatheter was filled with NBCA. Phase 2 (figure 4B) continued as jetting flow (short jet) with length of jet dependent on outer shell flow velocity and vessel diameter. Phase 3 (figure 4C) occurred when NBCA wetted the vessel wall and continued to roll off the vessel wall, sending droplets downstream so long as the glue remained liquid.

DISCUSSION

In this study, we sought to systematically characterize the factors that influence NBCA polymerization in both static and dynamic environments. The effect of pH and temperature on glue polymerization time is known.[27] However, a detailed quantification of their effect on glue polymerization has not been previously reported. The manufacturer of TruFill (Codman, USA) provided a polymerization time versus mixture graph in the Instruction For Use (IFU, see online supplementary figure). However, the exact test conditions were not specified apart from 'testing in static bovine plasma'.[28] Exposure to anions is the most common way to initiate polymerization in cyanoacrylates.[29] The hydroxide (OH^-) anion is ubiquitous in aqueous environments, present whenever there is H_2O. In the clinical setting, prior to glue injection, the microcatheter is thoroughly flushed with D5W (5% dextrose solution) with the common explanation that D5W does not contain any ions. From a basic chemistry standpoint,

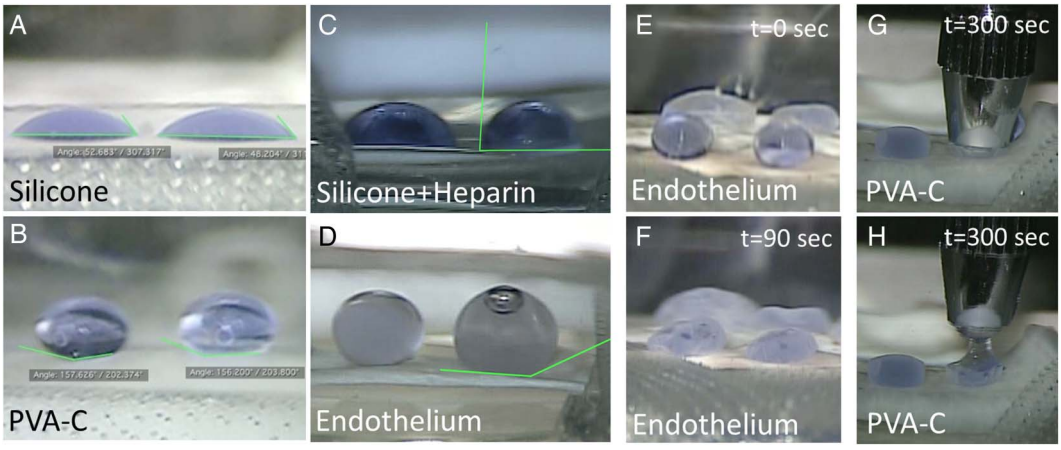

Figure 2 Contact angle measurements between n-butyl cyanoacrylate (NBCA)/Lipiodol droplets and different surfaces submerged in D5W at 37.5°C: silicone (A), polyvinyl alcohol cryogel (PVA-C) (B), silicone with heparin coating (C), and endothelium (D). Contact angle was significantly different between (A), (B), and (C) but not between (B) and (D) (pairwise t test). Endothelium possess additional catalytic properties that cause polymerization from the bottom up (E), effectively flattening the droplet as polymerization approached t_c of approximately 90 s for NBCA/Lipiodol droplets of 50/50 at pH=7.4 (F). Conversely, inert surfaces such as PVA-C can significantly delay polymerization once a shell forms. Indentation test on PVA-C surface at t=300 s (60/40 mix pH=7.4) showed incomplete polymerization with liquid center (G, H).

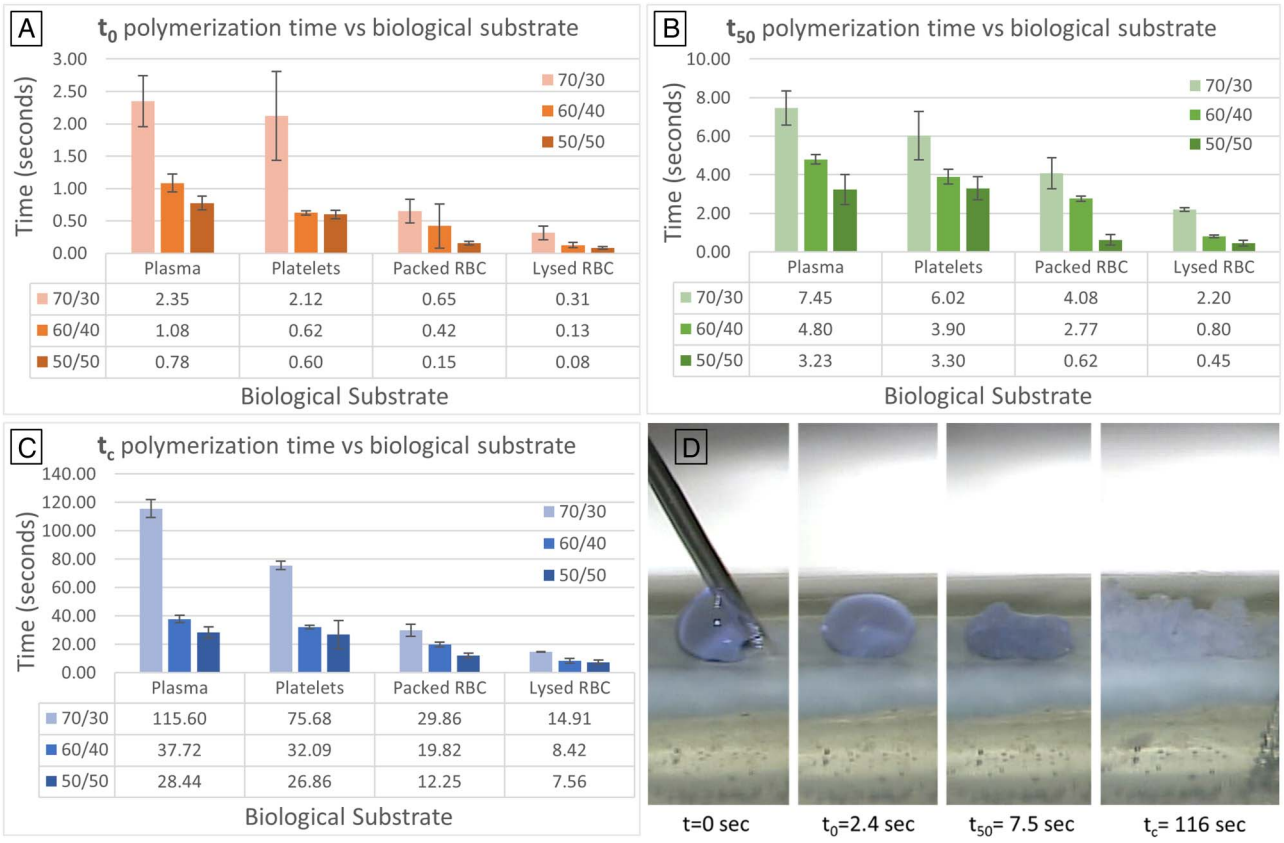

Figure 3 Effect of plasma, platelets, packed red blood cells (RBCs), and lysed RBCs on the time to onset of polymerization t_0 (A), time to 50% change in dimension of glue droplet t_{50} (B), and time to near complete (>95%) polymerization t_c (C) for Lipiodol/n-butyl cyanoacrylate (NBCA) formulations of 50/50, 60/40, and 70/30. The t_{50} times during exposure to packed RBCs better approximated the time frames seen clinically. (D) An example of t_0, t_{50}, and t_c times for 70/30 glue formulation during exposure to plasma. Note the progressive flattening followed by irregular morphological changes as the glue droplet polymerizes under the catalytic environment.

Table 1 Effect of live endothelium (no blood products) on polymerization times t_0, t_{50} and t_c (in seconds) for Lipiodol/NBCA formulations of 50/50, 60/40, and 70/30

	Glue mix: 50/50	Glue mix: 60/40	Glue mix: 70/30
t_0	0.6±0.3	1.6±0.4	13±3
t_{50}	8±2	72±6	614±31
t_c	98±4	416±6	1880±68

NBCA, n-butyl cyanoacrylate.

this is false as all solutions will contain ions. It is the relative concentration of these ions that will influence polymerization time, and D5W happens to be the most acidic isotonic solution used clinically with a pH of 4. This translates to the lowest concentration of OH^- groups available of any solution, resulting in the best prevention against polymerization.

The physical interaction of glue with different surfaces warrants caution when interpreting in vitro flow studies in existing scientific literature. Silicone is often used as a de facto vessel substitute in flow models. However, the behavior of glue on silicone is quite different from that of endothelium. Glue tends to spread more easily and stick to a silicone surface more readily, effectively 'coating' it due to the shallower contact angle. This reduces glue flow velocity and gives glue more time to polymerize in the silicone tubing. Therefore, studies employing silicone flow models to study glue embolization may overestimate the effect of glue polymerization (especially in the absence of any biological tissue) in achieving flow arrest.[30]

As a mock vessel surface, PVA-C provided the closest mimicry of endothelium. However, due to the lack of any catalytic activity, it was paradoxically more difficult to achieve flow arrest when injecting glue into PVA-C tubing. During polymerization, glue would form strong chemical bonds with the endothelial surface (based on our observations and current literature[31 32]) that could act as anchor points. Glue did not bond to PVA-C readily, further exacerbating the flow arrest problem. In vitro studies that employ mock vessels with hydrophilic surfaces should be interpreted in light of these findings.

The effects of biological substrates on glue polymerization time was significant and may help explain some of the discrepancies in previous studies that measured the polymerization time of NBCA in the in vitro setting. In one of the earliest papers, Stoesslein *et al*[24] measured the in vitro polymerization rate of NBCA/Lipiodol mixtures by bringing it into contact with citrated blood on a cover glass slip and visually observing polymerization. The authors did not further specify the criteria used to judge polymerization, although the values that they published appeared closer to t_c. Brothers *et al*[23] used a very different in vitro method where glue droplets were dripped into human plasma held in a transparent cup with a piece of newspaper underneath it. Opacification of the newspaper letters was defined as polymerization time, which is likely in between t_0 and t_{50}. Interestingly, both authors noted that in vivo studies

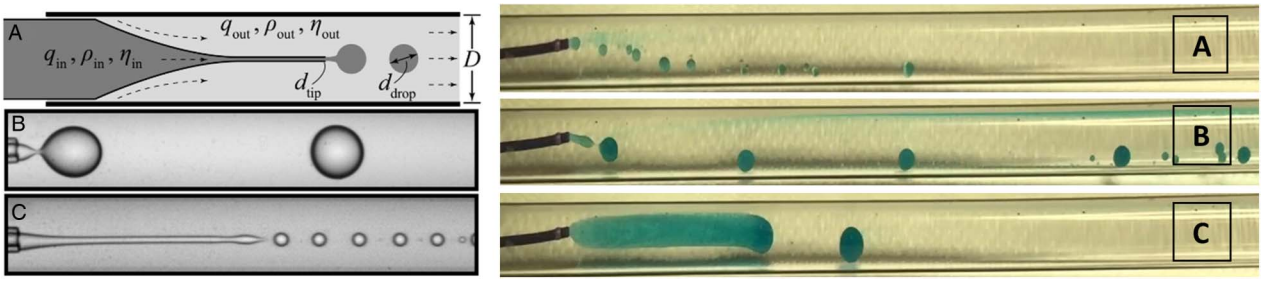

Figure 4 Left panels (A–C) are modified from the original publication by Utada *et al* (with permission), illustrating an ideal coaxial flow model (A) with transition from dripping (B) to jetting flow (C) as the core flow increases compared with shell flow.[26] Right panels (A–C) show screenshots of high speed video analysis (10× slow motion, see online supplementary video included) of n-butyl cyanoacrylate (NBCA) injection illustrating an initial period of dripping flow (A, <1 s) followed by transition to short jetting flow (B, 1–2 s). Different from the ideal model, wall effect emerges (C) at variable time points depending on microcatheter position (typically starting at approximately 3 s).

seemed to result in faster polymerization times compared with in vitro results.

A few explanations were entertained to explain the in vitro/in vivo discrepancy, such as mixing caused by bulk flow of blood and the greater availability of anions in vivo. In light of the results of this study, it was fortuitous that Stoesslein *et al* used whole blood as a biologic catalyst (albeit unknowingly). However, their values were closer to t_c (3.2, 4.7, and 7.5 s for 50/50, 33/66, and 25/75 formulations, respectively) than t_{50} as they were measuring near complete polymerization. Brothers *et al* on the other hand used plasma, which would give a slower polymerization rate. However, they chose opacification as the polymerization endpoint which occurs quite early, as seen in figure 3. This provided partial offset to the slower polymerization time in plasma and the study ended up with values (0.7, 2.5, 3, and 4 s for 100/0, 50/50, 33/66, and 25/75 formulations, respectively) that were closer to t_{50} in packed RBCs.

In the in vivo setting, glue polymerization cannot be measured directly, and operators must use other clues, such as nidus penetration or flow arrest as surrogate measures. This depends not only on polymerization time, but also on nidus morphology. Polymerization times may seem faster in vivo for two reasons: (1) the presence of biologic substrates (especially RBCs) and (2) interference from nidus or proximal feeders that allows partially polymerized glue to change/block flow before t_c is reached. It is for the second reason that we measured not only t_c, but also t_0 and t_{50}. Looking at the values of t_{50}, they appear to better approximate the time scales encountered clinically during embolization of AVMs (where contrast filling of the nidus can occur as quickly as 0.25–0.5 s). Glue does not need to fully polymerize to exert its effect, it just has to be hard enough to plug part of the nidus or feeding artery for stasis to occur.

Exposure to lysed RBCs appeared to result in the fastest glue polymerization time. The exact reason for this is unknown. It is known that amine groups from proteins can act as electron donors to initiate polymerization via a zwitterionic mechanism.[29] Cyanoacrylates have also been shown to form covalent bonds with proteins (ie, protein adducts) on exposure to biologic tissue.[33] Cell membrane components and charge probably do not fully explain this as both endothelium and platelets contain cell membranes and neither substrate showed polymerization times that were as rapid. Proteins and dissolved ions in general do not fully explain this either, as plasma contain abundant quantities of proteins (coagulation factors, immunoglobulins, albumin, etc) and ions, but does not have as rapid a polymerization time. As lysed RBCs resulted in even faster polymerization rates than whole RBCs, this leads us to surmise that RBC specific intracellular content plays the biggest role, and hemoglobin is highly suspect. More work will be needed to further delineate this.

High speed video analysis of microcatheter glue injection revealed that unlike the idealized flow model, wall interaction is an important factor to consider. Wall interaction causes smearing and sticking of liquid glue with possible formation of anchor points after polymerization occurs. The heparin coated silicone surface provides good light transparency but does not provide the same degree of hydrophilicity as endothelium. The smearing will likely be less prominent in an endothelial surface. However, endothelium does have some degree of catalytic activity and bonds to NBCA very well. This may partially explain the observation in prior histological studies of NBCA casts found at the vessel wall with Lipiodol droplets trapped near the center.[31 32] Therefore, premature feeding artery occlusion is still a concern even with a well adjusted glue formulation.

A partially formed adherent glue cast in the proximal feeder (due to the wall effect) could trigger more glue adhesion and polymerization, resulting in feeding artery occlusion before the nidus is fully embolized. The ‘wedge technique’ may help alleviate this problem; however, both the ‘sandwich’ and ‘full column’ techniques will be subject to wall effect if the microcatheter tip is parked some distance away from the nidus. The complex angioarchitecture of AVMs may preclude more proximal navigation in some instances, with some interventionalists occasionally using adjuncts to slow down blood flow for better control (temporary balloon occlusion, Valsalva, double catheter, adenosine, etc).

CONCLUSION

PVA-C provides a better vessel substitute with respect to physical surface properties; however, it does not possess any catalytic activity encountered in the in vivo setting. Biological catalysts play a substantial role in increasing polymerization rate, with exposure to RBCs being the most important factor. Clinically relevant polymerization times likely fall somewhere closer to t_{50} than to t_c which may help optimize glue formulation selection. Clinically, continuous flushing of the microcatheter with D5W provides an acellular/plasma free environment with the lowest pH to prevent unanticipated early polymerization which is most likely related to contamination with RBCs. High speed video analysis reveals that microcatheter injection exhibits dripping to jetting transition with an important additional phase of vessel wall interaction. A refined understanding of the polymerization behavior of NBCA could help reduce embolization related complications.

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Contributors BHW: conceptual design, data acquisition, data analysis and interpretation, and manuscript composition. MRB: conceptual design of subcomponents of the project and manuscript revision. DHL and DMP: helped with interpretation of portions of the results given extensive clinical experience with NBCA, and manuscript revision. SPL: conceptual design, interpretation of the results, manuscript revision, and critical appraisal.

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